Bacterial infections of the respiratory tract and their pharmacological treatment

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Abstract

Bacterial infections of the respiratory tract contribute to significant morbidity and mortality worldwide. Early recognition of lower respiratory tract infections is fundamental for the management and prevention of complications such a sepsis. Common respiratory infections such as community-acquired, hospital-acquired pneumonia, atypical bacterial infection, and acute infective exacerbations of chronic disease such as chronic obstructive pulmonary disease and bronchiectasis are caused by a wide range of pathogens which can be treated in the community or in the hospital setting based on assessment of severity. Antibiotics are by far the most commonly used pharmacological intervention in the management of bacterial infections. Antibiotics have different and unique mechanisms of action against bacteria and several guidelines exist to direct treatment of chest infections. However, with inappropriate use of antibiotics, the resistance of bacteria to antimicrobials has seen significant growth globally, causing concern to the public health. Other pharmacological interventions for the management of infections and sepsis are in the development phase.

Keywords Antibiotics; bronchiectasis; COPD; pneumonia; sepsis; tuberculosis

Royal College of Anaesthetists CPD Skills Framework: ICM and emergency management

Learning objectives

After reading this article, you should be able to:

- describe the burden of common infections of the respiratory tract
- describe the assessment and diagnostic tools of sepsis and common infections of the respiratory tract
- describe pharmacological interventions, and the basis of their mechanisms of action, used in the treatment of infections of the respiratory tract

Background

Infections of the respiratory tract are a leading cause of morbidity and mortality worldwide. In 2012, 345 in 100,000 people had at least one episode of pneumonia, and between 2001 and 2010 214 for every 10 million died of it in the UK, disproportionately affecting older people. There are sparse national level data on the burden of lower respiratory tract infection, particularly following the coronavirus disease (COVID-19) pandemic.[1,2]

In this article, we discuss common infections of the respiratory tract, their assessment, diagnosis and pharmacological interventions.

Assessment and recognition

The diagnosis of a chest infection at the bedside requires recognition of various presenting signs and symptoms. Cough, with or without sputum, is frequently seen, together with breathlessness, chest pain, fever, sweating, and confusion can be seen, particularly in the elderly. Additionally, enquiring about comorbid illnesses, smoking history, and risk of exposure to respiratory pathogens is important.

Assessment includes examining the patient's respiratory system and looking for systemic features of sepsis. Frequently observed features include hypoxia, tachypnoea, hypotension, confusion, rhonchi, wheeze, bronchial breathing, and high temperature.

Nonetheless, the pattern of presentation varies between different types of causative pathogens and patient-groups, and it can be difficult to identify a specific constellation of signs and symptoms, hence, clinical judgement coupled with appropriate investigations can facilitate early diagnosis and management. Radiological imaging, routinely a chest X-ray (CXR), is useful for confirmation of the diagnosis. Imaging is also useful in identifying or excluding other conditions in the differential diagnosis which have similar presentation, such as pneumonitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS) and congestive cardiac failure. Microbiological testing of blood, sputum, and nasopharyngeal specimen samples is necessary in patients with moderate and severe infection or those with underlying chronic respiratory disease for tailoring of treatment. Testing for biochemical markers such as C-reactive protein, white cell count, and procalcitonin can aid in diagnosis, assessing the severity of infection, and monitoring response to treatment, with evidence supporting using procalcitonin to guide cessation of antibiotics.[3–5]

Chest infections and the choice of pharmacological treatment

Community-acquired pneumonia (CAP)

CAP is an acute infection of the lungs caused by a range of pathogens acquired outside of hospital, leading to accumulation of fluid and inflammatory cells, and compromising function of lung tissue. With an annual incidence of 5–10 per 1000 adult population, CAP has a 22–42% hospital admission rate, and

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mortality rate ranging from 20% to 50% amongst patients requiring intensive care treatment.[3]

Diagnosis of CAP relies on a high index of suspicion and assessment should look for signs and symptoms with a higher probability of indicating CAP, including tachypnoea, wheeze, low oxygen saturations, fever, hypotension, tachycardia, and changes in level of consciousness.[3]

A wide range of bacteria can cause CAP, and identifying a likely causative microorganism depends on factors such as the severity of illness, age, and comorbidities. The leading causative agent is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, *Staphylococcus aureus*, group A streptococci, *Moraxella catarrhalis*, and atypical bacteria. Less commonly, CAP is caused by organisms which are not covered by standard empirical treatment, such as *Pseudomonas aeruginosa* (particularly in chronic lung disease), Enterobacteriaceae extended spectrum β-lactamase, and meticillin-resistant *Staph. aureus* (MRSA).[3]

Determining the severity of CAP is important to guide treatment. The widely used CURB-65 score is a six-point system based on presence of confusion, urea level (>7 mmol/litre), respiratory rate (≥30 breaths/minute), blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg), and age (≥65 years), to stratify patients with CAP into groups of low (score of 0 or 1), intermediate (score of 2), and high risk of mortality (score of ≥3). The British Thoracic Society (BTS) recommends using the CURB-65 score together with clinical judgement in the assessment of severity, considering referral to hospital for those with score of 1 or 2, and urgent hospitalization for those with a score of 3 or more.[3,6]

The choice of antibiotic is ideally guided by local policy which would be based on considerations of local prevalence of pathogens and patterns of antimicrobial resistance. See Table 1 for the BTS recommendations. Decisions on the duration of treatment, switching to alternative antibiotics in case of failure of initial therapy, and switching to oral antibiotics depends on clinical judgement on the patient's progress, complications, and identification of a specific causative pathogen.[6,7]

Common complications including the development of lung abscess, parapneumonic effusion, and empyema warrant investigating for bacteria such as *Staph. aureus*, Gram-negative bacilli, and *Streptococcus milleri*, as well as considering prolonged antibiotic treatment.[3,6]

Atypical bacterial infections

Atypical bacteria like *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* (also known as *Chlamydia pneumoniae*), and *Legionella pneumophila* can cause CAP often referred to as atypical pneumonia. Their prevalence varies between different areas and is largely underreported.

Mycoplasma pneumoniae is a frequent cause of pneumonia in both children and adults and tends to cause outbreaks in semi-closed locations such as universities and schools, spreading through respiratory droplets. Although it can present like other causes of CAP, a substantial proportion of patients with *M. pneumoniae* present with extrapulmonary involvement, features include haemolysis (usually subclinical), dermatitis, and arthritis. It has also been associated with nervous system involvement, most commonly encephalitis, worsening of asthma symptoms, and less commonly with pericarditis and myocarditis *M. pneumoniae* can be challenging to diagnose, and standard oral β-lactam therapy does not treat it. If necessary, testing is with sputum polymerase chain reaction (PCR) or nuclear acid amplification tests (NAATs) can be done on specimens of nasopharyngeal swabs, sputum, or bronchoalveolar lavage (BAL). Treatment is described in Table 1.

Pneumonia is the commonest form of infection caused by *Legionella*, known as Legionnaire's disease. It can rarely cause infections such as cellulitis, meningitis, and endocarditis. The prevalence of *L. pneumophila* infection varies seasonally increasing in hot humid weather and is known to cause outbreaks in buildings with contaminated water supplies, hence, it is important to explore risk factors for exposure if suspected. It can be suspected in the presence of associated gastrointestinal symptoms, hyponatraemia and elevated liver transaminases levels. Early testing of *L. pneumophila* antigen in urine (highly specific and has a pooled sensitivity of about 74%) is beneficial in severe cases or when an outbreak is suspected, and further testing includes detecting sputum Gram-staining and culture, NAATs and serology. See Table 1 for treatment.

Chlamydophila pneumoniae typically presents similar to other forms of CAP, and infection is usually mild. Treatment is similar to that of *M. pneumoniae*.[6,8]

Hospital-acquired pneumonia (HAP)

Hospital-acquired pneumonia (HAP) is an infection of the lungs acquired after 48 hours of admission to hospital. The UK National Institute for Health and Care Excellence (NICE) excludes ventilator-associated pneumonia from this definition. It is associated with high mortality and is common amongst patients with prolonged hospital stay, following surgery, and in intensive care units (ICU). Most common causative organisms are MRSA, *P. aeruginosa*, and other Gram-negative bacteria.

HAP is suspected in the presence of features of lower respiratory tract or systemic infection. Prompt treatment is essential to reduce the risk of morbidity and death, and it is based on an evaluation of severity using clinical judgement and considerations of age, comorbidities, and history of colonization with drug resistant bacteria. Duration of intravenous treatment required for high severity infection is guided by improvement, and antibiotics can be switched to oral options as the patient improves.

Ventilator-associated pneumonia (VAP) is a form of pneumonia that occurs in hospital 48 hours after endotracheal intubation. It is a common infection in ICUs with a variable incidence and has an attributable mortality of about 10%. Multiple risk factors have been reported for the development of VAP which requires a high suspicion index to diagnose, usually with a change to tracheal secretions/aspirates, fever, changes in ventilator mechanics or a change to biochemical markers or imaging. *P. aeruginosa* and *Staph. aureus* are the most reported causative organisms. There is no consensus on diagnostic clinical or radiological criteria. However, VAP should be suspected when imaging shows new or progressive lung infiltrates and there are supportive clinical findings of infection. Microbiology testing of respiratory samples is essential to guide targeted antibiotic therapy, where initial therapy is empirical antibiotics. Some evidence suggests the use of prophylactic antibiotics (selective decontamination of the digestive tract (SDD)) may reduce the risk of VAP in ventilated patients, however this is not widely used.[9,10]

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Common bacterial infections of the chest and the recommended choices of empirical antibiotics

Type of infection	First-line treatment	Alternative treatment (e.g. in penicillin allergy)
Community-acquired pneumonia		
Low severity (CURB-65 of 0,1)	Oral amoxicillin 500 mg tds, for 5 days	Oral doxycycline 200 mg once then 100 mg od or clarithromycin 500 mg bd, for 5 days
Moderate severity (CURB-65 of 2)	Oral amoxicillin 500 mg—1 g tds + clarithromycin 500 mg bd IV amoxicillin 500 mg tds or benzylpenicillin 1.2 g qds + clarithromycin 500 mg bd	Oral doxycycline 200 mg once only then 100 mg od, or levofloxacin 500 mg od, or moxifloxacin 400 mg od
High severity (CURB-65 of 3 or more)	IV co-amoxiclav 1.2 g tds + IV clarithromycin 500 mg bd	IV benzylpenicillin 1.2 g qds + either IV levofloxacin 500 mg bd or IV ciprofloxacin 400 mg bd, OR IV cefuroxime 1.5 g tds or IV cefotaxime 1 g tds or IV ceftriaxone 2 g od, plus IV clarithromycin 500 mg bd
Mycoplasma pneumoniae		
Low severity	Oral doxycycline 200 mg once only then 100 mg od, or clarithromycin 500 mg bd, or levofloxacin 500 mg od, for 5 days.	
Moderate to high severity	IV cefuroxime 1.5 g tds or IV cefotaxime 1 g tds or IV ceftriaxone 2 g od, plus IV clarithromycin 500 mg bd OR IV levofloxacin 500 mg bd.	
Legionella pneumophila		
Low to moderate severity	Oral or IV levofloxacin 750 mg od for 7 days, or oral ciprofloxacin 750 mg bd for 7 days (400 mg tds if given IV), or oral clarithromycin 500 mg bd for 14 days	Oral doxycycline 200 mg once only followed by 100 mg bd for 14 days
High severity	Combination of IV levofloxacin or IV ciprofloxacin (for 7—14 days) with oral clarithromycin for 14—21 days	
Hospital-acquired pneumonia		
Low severity	Oral co-amoxiclav 500/125 mg tds for 5 days	Oral doxycycline 200 mg once only, then 100 mg od, or cefalexin (caution in penicillin allergy) 500 mg bd or tds, or co-trimoxazole 960 mg bd for each option for a total of 5 days
High severity	IV piperacillin with tazobactam 4.5 g tds (consider adding teicoplanin or vancomycin if suspected or confirmed MRSA infection)	IV levofloxacin 500 mg bd.
Aspiration pneumonia		
(in hospital)	IV co-amoxiclav 1.2 g tds, or IV piperacillin with tazobactam 4.5 g tds if high risk of anaerobic infection	IV levofloxacin 500 mg bd add oral or IV Metronidazole if high risk of anaerobic infection
Acute exacerbation of COPD		
Low severity	Oral amoxicillin 500 mg tds or co-amoxiclav 500/125 mg tds for 5 days	Oral doxycycline 200 mg once only, then 100 mg od, or clarithromycin 500 mg bd, or co-trimoxazole 960 mg bd (sensitivity guided) for 5 days
High severity	IV amoxicillin 0.5—1 g tds, or co-amoxiclav 1.2 g tds, or piperacillin with tazobactam 4.5 g tds	IV clarithromycin 500 mg bd, or co-trimoxazole 960 mg bd
Acute exacerbation of bronchiectasis (all for 14 days)		
First presentation, or known *P. aeruginosa*, *Klebsiella*, or *Enterobacter* infection	Low severity: oral ciprofloxacin 500—750 mg bd High severity: 14 days of IV ceftazidime 2 g tds, or piperacillin with tazobactam 4.5 g tds ± IV gentamicin	IV aztreonam 2 g tds or meropenem 2 g tds ± IV gentamicin

(*continued on next page*)

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Table 1 (*continued*)

Type of infection	First-line treatment	Alternative treatment (e.g. in penicillin allergy)
MRSA	Low severity: oral doxycycline 100 mg bd, or rifampicin 450 mg od (weight < 50 kg) to 600 mg (weight > 50 kg) High severity: IV vancomycin 1 g bd	Low severity: oral trimethoprim 200 mg bd, or linezolid 600 mg bd high severity: IV meropenem 400 mg od, or linezolid 600 mg bd for
Staphylococcus aureus (meticillin-sensitive)	Oral flucloxacillin 500 mg qds, or co-amoxiclav 500/125 mg tds	Oral doxycycline 100 mg bd, or clarithromycin 500 mg bd
Haemophilus influenzae (β-lactamase positive), *Moraxella catarrhalis*	Oral co-amoxiclav 500/125 mg tds	Oral doxycycline 100 mg bd, or oral ciprofloxacin 500—750 mg bd
H. influenzae (β-lactamase negative), *Streptococcus pneumoniae*	Oral amoxicillin 500 mg tds (upto 3 g bd for *H. influenzae*)	Oral doxycycline 100 mg bd (ciprofloxacin oral dose is an option for *H. influenzae*)

bd, twice daily; COPD, chronic obstructive pulmonary disease; IV, intravenous; MRSA, meticillin-resistant *Staphylococcus aureus*; od, once daily; qds, four times daily; tds, three times daily. Doses described are for adults without contraindication and assume normal liver and kidney function.

Table 1

Aspiration pneumonia (AP)

Aspiration pneumonia (AP) refers to alveolar injury and systemic inflammation resulting from aspiration of oropharyngeal or gastrointestinal secretions. Aspiration of an amount sufficient to cause AP is usually associated with abnormal swallowing and some patient groups are at more risk. AP has a mortality of about 10—15% in hospital, and when swallowing impairment is suspected, the patient should be assessed by specialist speech and language therapist, and the wider clinical team should work to develop a plan to prevent AP. Oral examination and maintaining good oral hygiene is essential in the prevention of AP, particularly in ICU settings. There is no sufficient evidence to support the use of pharmacological interventions to prevent AP, although some studies have shown benefit in the use of angiotensin-converting enzyme (ACE) inhibitors in Chinese and Japanese patients following stroke. Metoclopramide has also shown some benefit in patients fed via nasogastric tube following stroke. There is an association between the use of acid-suppressive medications and AP, CAP and VAP, as the loss of gastric acid results in a high bacterial load in gastric contents and therefore in the lung if aspirated.

When acquired in hospital AP is likely to extend the array of possible causative bacteria that is associated with HAP/VAP. Hence, it is very important to promptly obtain microbiological specimens. Antibiotic treatment should follow local guidelines, and unless a patient is deemed to be at high risk of anaerobic infection, such as in patients with dental disease, lung abscess, or empyema, the BTS does not recommend covering for those organisms.[11,12]

Chronic obstructive pulmonary disease (COPD)

Bacterial infection, mostly with *H. influenzae*, *Strep. pneumoniae*, and *M. catarrhalis*, is a recurrent trigger of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and worsening symptoms of COPD from the patient's usual stable state.

In order to determine the severity and place of treatment, assessment of suspected AECOPD should include an enquiry about severity of symptoms, change to the colour or volume of sputum, frequency of previous exacerbations. Microbiology testing of sputum samples is valuable, particularly in patients with recurrent use of antibiotics. Clinical judgement should be used to determine the choice and route of initial antibiotics until therapy can be tailored with microbiology guidance.[13]

Exacerbation of bronchiectasis

The irreversible injury and dilatation of the bronchi seen in bronchiectasis is a harbour to recurrent or persistent infections of the bronchi. In non-cystic fibrosis patients, about 34% have no significant comorbidity; however, some disease groups have been associated with bronchiectasis such as asthma, COPD, human immunodeficiency virus (HIV) infection, rheumatoid arthritis, allergic bronchopulmonary aspergillosis, and α-1 antitrypsin deficiency. A single or multiple bacteria can lead to infection and exacerbation of symptoms, notably *P. aeruginosa* and *H. influenzae* are the commonest Gram-negative organisms together with *Klebsiella pneumonia*, *M. catarrhalis*, and *Burkholderia cepacia*. Gram-positive organisms are also commonly isolated including *Staph. aureus*, *Strep. pneumoniae*, and β-haemolytic streptococci.

Acute exacerbations of bronchiectasis are characterized by changes in sputum viscosity, colour or volume, haemoptysis, or worsening cough, shortness of breath and increased fatigue. All patients, prior to starting antibiotics, should have previously isolated bacteria reviewed and new sputum samples sent for Gram stain and culture to guide further antibiotic therapy. Samples should also be sent for mycobacterial culture because non-tuberculous mycobacteria can cause exacerbations too. In patients with previously isolated *P. aeruginosa*, or a first growth, the BTS guidelines recommend at least 14 days of antibiotics (Table 1). Aminoglycosides are to be used cautiously considering the risk of ototoxicity and nephrotoxicity Patients with a bronchiectasis exacerbation with features of severe infection necessitating ITU admission should have antibiotic cover for the last known bacteria isolated. If there are no known bacteria and the patient is very unwell then cover for both *Pseudonmonas* and *Staph. aureus*, preferably with two agents, should be commenced pending microbiology results.[14]

Secondary bacterial infections of the lung

Bacterial infections can complicate other infections of lung such as with severe acute respiratory syndrome coronavirus 2

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(SARS-CoV-2) and influenza virus. Data prior to the COVID-19 pandemic suggest an increase in severity of illness, morbidity, and mortality in patients with secondary bacterial infections and coinfections. Common respiratory pathogens reported to cause secondary infections include *Strep. pneumoniae*, *P. aeruginosa*, MRSA, *Klebsiella pneumoniae*, *Haemophilus influenza*, *Enterococcus*, and *Acinetobacter*. More evidence is needed to understand likely alterations in the burden and patterns of secondary bacterial infections.[15]

Pulmonary tuberculosis

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is a global health issue with an estimated 10 million people developing the illness annually and 1.5 million related deaths worldwide. Patients with a latent infection have normal CXR appearance, a positive tuberculin skin test or interferon γ release assay, and are non-infectious. About 10% of those patients develop active TB, and the risk of reactivation is higher in the first 2 years following exposure and in conditions leading to immunosuppression, especially untreated HIV infection.

In the presence of risk factors (including birth in a high incidence country, previous prison history, homelessness), known TB exposure and suggestive symptoms such as fever, chronic cough, haemoptysis, and unexplained weight loss, patients should be investigated for possible TB. In ICU, patients may present atypically with features of TB meningitis or pericarditis, both of which carry high mortality. Three deep, spontaneously produced or induced sputa or BAL samples should be sent for mycobacterial staining and culture. Chest X-ray can be suggestive and if miliary tuberculosis is present investigations for disseminated tuberculosis should be completed including brain imaging and lumbar punctures. Pleural fluid specimens may be required if pleural TB is suspected as well as biopsies or aspirates of lymph nodes for intrathoracic mediastinal disease. PCR/NAAT tests can aid in more rapid diagnosis and rapid identification of drug resistance in those at risk.

Urgent referral to the TB multidisciplinary team is necessary. Quadruple therapy with isoniazid with rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months then isoniazid with pyridoxine and rifampicin for a further 4 months should be commenced unless there is evidence of resistance or extrapulmonary disease such as central nervous system involvement. Most patients with rifampicin resistance carry a multi-drug-resistant infection, and treatment duration, guided by experts, is extended to 9–24 months.[16,17]

Epiglottitis

Patients with an infection of the epiglottis are usually children aged 2–6 years old, but it can affect all age groups. Epiglottitis is most commonly caused by *H. influenzae*, but also by other bacteria and viruses. Its prevalence has reduced since the introduction of the *H. influenzae* type b (Hib) vaccine. Patients classically present with high fever, drooling, breathlessness, dysphagia and reduced oral intake. Adults may describe symptoms such as odynophagia and sore throat. If untreated it can rapidly progress to airway compromise and complete airway obstruction. Lateral neck X-ray typically shows an enlarged epiglottis (thumbprint sign), and laryngoscopy confirms the diagnosis. Maintenance of the airway is the mainstay of treatment. Intubation is usually required in children and in about 11% of adults together with intravenous empirical β-lactam or glycopeptide antibiotic.[18,19]

Pharmacological therapy

Mechanisms of action of antibiotics

Antibiotics have distinct ways that lead to suppression of activity (bacteriostatic) or death (bactericidal) of bacteria. A key target for antimicrobial agents is the bacterial cell wall, and peptidoglycan, the main structure in the cell wall, is a target for antibiotics such as β-lactams (e.g. penicillins) by binding to penicillin-binding proteins and glycopeptides (e.g. vancomycin, teicoplanin) by acting on transpeptidase and destabilizing peptidoglycan. Antibiotics such as macrolides (e.g. clarithromycin), aminoglycosides (e.g. gentamicin, amikacin), and tetracyclines (e.g. doxycycline) inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome, leading to mistranslation and growth inhibition. Chloramphenicol, on the other hand, binds to the 50S subunit, preventing the elongation step of protein synthesis. Nucleic acid synthesis is another target for antimicrobial agents, with fluoroquinolones (e.g. ciprofloxacin, levofloxacin) inhibiting DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria. Inhibition of these enzymes leads to abnormal DNA formation and cell death. Sulphonamides inhibit folate synthesis such as with trimethoprim via inhibiting dihydrofolate enzyme.[20]

Pharmacokinetics and pharmacodynamics of antibiotics

The outcome of antibiotic treatment of an infection with a susceptible organism is influenced by patient factors, such as their comorbidities and physiological reserve, the severity of the illness, and drug related factors. Under strict in vitro conditions, the lowest concentration of an antibiotic, in milligrams or micrograms per litre, required to completely inhibit visible bacterial growth of a test strain is referred to as the minimum inhibitory concentration (MIC). The MIC has the value of assessing the degree of bacterial susceptibility or resistance to the action of an antibiotic, as well as the likelihood of clinical efficacy.

Antibiotics differ in the mode in which they can effectively kill bacteria. Together with the MIC, other parameters that can predict the therapeutic efficacy of an antibiotic include the maximum concentration (CMax)/MIC ratio, the area under the concentration–time curve (AUC)/MIC ratio, and the time during which the antibiotic concentration exceeds the MIC (T>MIC) (Figure 1). For instance, penicillins, cephalosporins, macrolides, and carbapenems are examples of time-dependent antibiotics in bacterial killing, given in frequent doses, as their outcome is improved with longer durations where the level is above the MIC with a maximized T>MIC at the infection site. On the other hand, concentration-dependent antibiotics, like aminoglycosides and fluroquinolones, have better action with high concentrations given in infrequent doses, even for relatively shorter times, maintaining high C CMax/MIC or AUC/MIC ratios. Monitoring of drug levels for concentration dependent antibiotics can be necessary to avoid toxicity and subtherapeutic levels.

Critical illness and renal and hepatic dysfunction have an influence on the pharmacokinetics of antibiotics and the clinical response to treatment. This may lead to suboptimal antibiotic exposure which is related to alterations in the antibiotic volume

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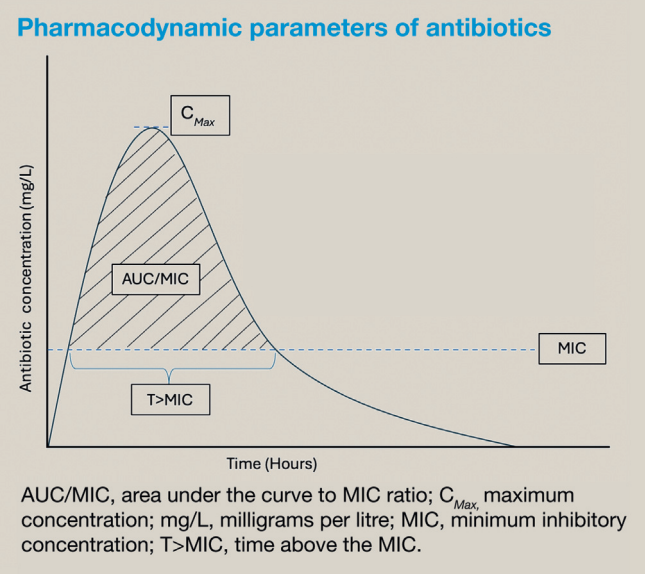
Pharmacodynamic parameters of antibiotics
C Max
AUC/MIC
MIC
T>MIC
Antibiotic concentration (mg/L)
Time (Hours)
AUC/MIC, area under the curve to MIC ratio; C Max, maximum concentration; mg/L, milligrams per litre; MIC, minimum inhibitory concentration; T>MIC, time above the MIC.

Figure 1

of distribution, protein binding, and clearance amongst patients in ICU who are prone to infections with less susceptible organisms, ultimately leading to poor therapeutic outcomes. The influence of these pathophysiological alterations varies between time- and concentration-dependent types, an area where more research is undergoing.[20–25]

Antimicrobial resistance

Antimicrobial resistance (AMR) predates the discovery of antibiotics. AMR can be intrinsic to the bacteria where all strains of a bacterial species are not susceptible to the antibiotic class action. Bacteria can acquire resistance by de novo mutation or by transfer of resistant genes from another organism. This horizontal transfer of genetic material encoding mechanisms of resistance, such as with plasmids, is of greater concern to the public health.

Mechanisms of resistance include development of an antibiotic-destroying enzyme (e.g. β-lactamases resistance in *Escherichia coli*) that destroy the antibiotic, modification of the antibiotic (e.g. aminoglycosides resistance in *P. aeruginosa*), acquisition and upregulation of an efflux pump to remove the antibiotic from the bacterial cell (e.g. efflux of fluoroquinolones in *Staph. aureus*), and altering the target site of antibiotic action (e.g. macrolide resistance in Gram-positive bacteria) (Figure 2).

It is estimated that AMR has led to 1.27 million and contributed to 4.95 million deaths worldwide in 2019. Prevention and appropriate use of antibiotic stewardship are central in tackling this global health threat.[26–28]

Steroids

Clinical appropriateness and the effect of using steroids for treatment of pneumonia remains a matter of controversy. The rationale for their use is a reduction in the inflammatory response, resulting in a reduction in the progression to further lung injury, ARDS and death. Steroids may decrease the likelihood of requiring intubation and ICU length of stay in severe pneumonia. In CAP some studies suggest a mortality benefit whereas others don't. Recently, in severe CAP, Meduri et al. found no benefit from low-dose methylprednisolone. By contrast, another trial by Dequin et al. showed that early treatment with hydrocortisone in patients admitted to ICU with severe CAP was associated with a reduction in 28-day mortality. The lack of a clear answer has led to diverse interpretations of the available literature with different recommendations from different international societies. Large platform

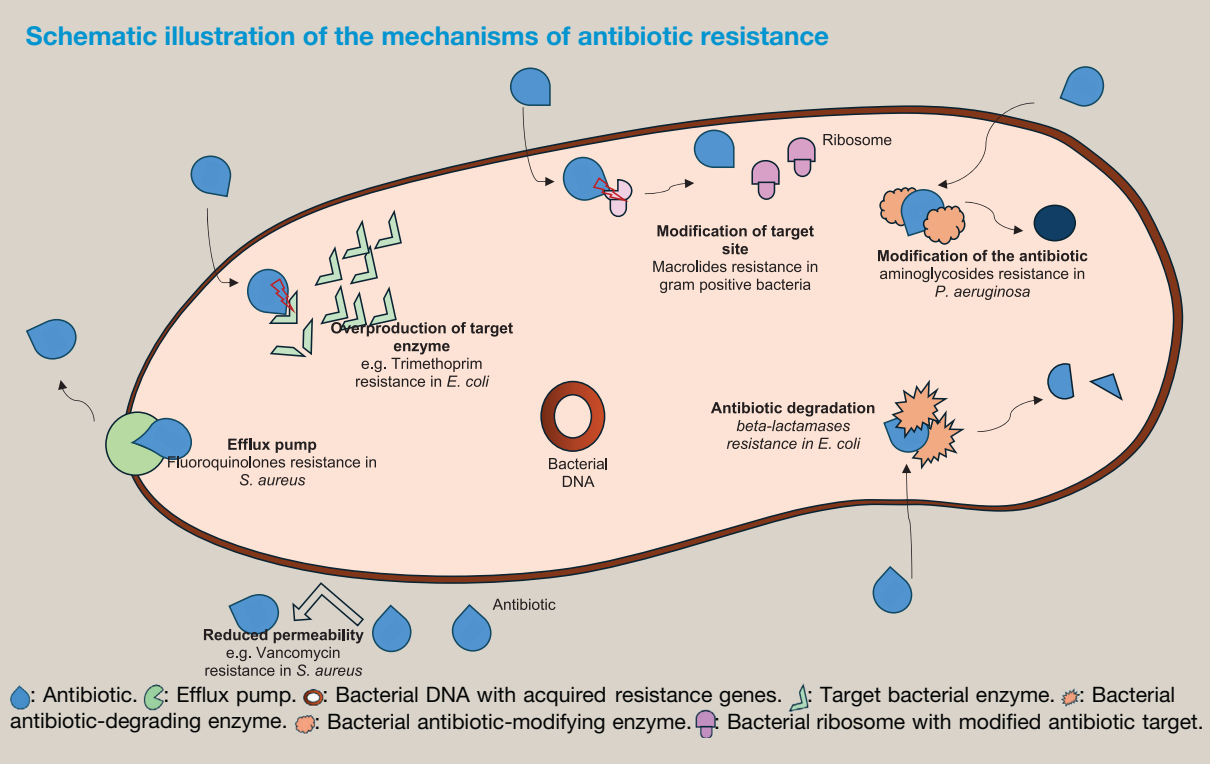
Schematic illustration of the mechanisms of antibiotic resistance
Ribosome
Modification of target site
Macrolides resistance in gram positive bacteria
Modification of the antibiotic
aminoglycosides resistance in P. aeruginosa
Overproduction of target enzyme
e.g. Trimethoprim resistance in E. coli
Efflux pump
Fluoroquinolones resistance in S. aureus
Bacterial DNA
Antibiotic degradation
beta-lactamases resistance in E. coli
Antibiotic
Reduced permeability
e.g. Vancomycin resistance in S. aureus
: Antibiotic. : Efflux pump. : Bacterial DNA with acquired resistance genes. : Target bacterial enzyme. : Bacterial antibiotic-degrading enzyme. : Bacterial antibiotic-modifying enzyme. : Bacterial ribosome with modified antibiotic target.

Figure 2

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studies are currently ongoing which will help answer this ongoing debate.[29–31]

Potential new drug targets in management of sepsis

The pathogenesis of sepsis involves complex processes. Currently, there are no effective therapeutic drugs for the treatment of sepsis. Drug development is exploring options on regulating the various processes involved in the systemic response to sepsis. For example, inflammatory imbalance targeted through cytokine antagonists (e.g. afelimomab, CytoFab) and PRR antagonists (e.g. TAK-242). Coagulation disorders are also being addressed (e.g. with recombinant human soluble thrombosis regulators).[29,32] ◆

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